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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/696,867	10/25/2000	Mary E. Brunkow	240083.501D6	2612

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EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/696,867	BRUNKOW ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35,40,42,44,46 and 47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35,40,42,44,46 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response filed on 09/03/03 has been acknowledged.
Claims 34, 36-39, 41, 43 and 45 are canceled.
Claims 46-47 are newly filed.
Claims 35, 40, 42 and 44 are amended.
Claims 35, 40, 42,44 and 46-47 are pending and are examined in this office action.

*Applicants are required to follow Amendment Practice under revised 37 CFR §1.121 (http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm). The fax phone numbers for the organization where this application or proceeding is assigned is **703-872-9306**.*

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Claim Rejections - 35 USC § 112

Claim 35, 40, 42,44 and 46-47 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic Scurfy mouse whose somatic and germ cells express a transgene comprising a 30kb fragment of normal genomic DNA, including ~7kb coding region of Fkh^{sf} gene as well as ~20kb of upstream flanking sequence and ~4kb of down stream sequences that contain a sequence encoding mouse Fkh^{sf} protein wherein the expression of exogenous Fkh^{sf} transgene results in reduction of T-lymphocyte proliferation in the scurfy mouse, does not reasonably provide enablement for any transgenic mouse, whose cells express an Fkh^{sf} transgene encoding mouse Fkh^{sf} (SEQ ID NO:1) or human Fkh^{sf} (SEQ ID NO:3), wherein the expression of the Fkh^{sf} transgene results in reduction of T-lymphocyte proliferation in the mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons of record as set forth in the office action mailed on 06/03/03.

Nature of Invention:

Invention relates to a transgenic S*curfy mouse (mut. Fkh^{sf} gene)* wherein the expression of the Fkh^{sf}-transgene comprising a normal Fkh^{sf} gene results in reduction of T-lymphocyte proliferation in the mammal.

Breadth of Claims and Guidance Provided by the Inventor:

The scope of invention as claimed encompasses a transgenic mouse whose cells express an Fkh^{sf} transgene encoding mouse Fkh^{sf} (SEQ ID NO:2) or human Fkh^{sf} (SEQ ID NO:4), wherein the expression of the Fkh^{sf} transgene results in reduction of T-lymphocyte proliferation in the transgenic mouse.

The specification teaches isolation of mouse (SEQ ID NO:1) and human (SEQ ID NO:3) Fkh^{sf} DNA sequences (spec. page 32, example-1). The specification teaches that a two base pair insertion in normal Fkh^{sf} transgene resulted in *Scurfy phenotype* in mice (page 32, line 20-25). At best the specification only teaches the generation of transgenic mouse *(Scurfy mouse)* wherein a 30 kb fragment of the normal genomic DNA, including the ~7 kb coding region of the Fkh^{sf} gene, as well as ~20 kb of upstream flanking sequences and ~4 kb of downstream sequences (FIG. 5) was microinjected into mouse one-cell embryos. Five individual founder animals were generated (spec. page 33, lines 9-17). The specification further disclosed that analysis of *sf (Scurfy)* progeny reviled that the expression of Fkh^{sf} transgene in *sf* mice over come the lymphoproliferative defect found in scurfy mice. The specification concluded that addition of the normal Fkh^{sf} gene can overcome the defect found in scurfy mice, confirming that the mutation in the Fkh^{sf} gene is the cause of *Scurfy disease* (spec. page 33, lines 25-27, figures 6-8).

Besides a transgenic mouse *(Scurfy mouse) whose genome encodes* a 30 kb fragment of the normal genomic DNA, including the ~7 kb coding region of the Fkh^{sf} gene, as well as ~20 kb of upstream flanking sequences and ~4 kb of downstream sequences, the specification as filed fails to disclose any other transgenic mouse whose genetic or somatic cells express a Fkh^{sf} transgene encoding mouse Fkh^{sf} (SEQ ID NO:2) or human Fkh^{sf} (SEQ ID NO:4), wherein the expression of the Fkh^{sf} transgene results in reduction of T-lymphocyte proliferation in the mammal. The specification as

filed fails to disclose that a transgene encoding the mouse Fkh^{sf} (SEQ ID NO:2) or human Fkh^{sf} (SEQ ID NO:4) alone (without any promoter), would lead to the reduction of T-lymphocyte proliferation in the transgenic mouse as claimed. In addition, the specification fails to provided any substantial evidence that a transgene encoding human Fkh^{sf} (SEQ ID NO:4) would replace the function of normal mouse Fkh^{sf} gene, since human and mouse Fkh^{sf} polypeptide are only 87% identical.

State of Art and Predictability:

The earlier office action clearly provided the evidence that the phenotype of an animal is determined by a complex interaction of genetics and environment. (Wood. Comp. Med. 50(1): 12-15, 2000, see page 12*; ref. of record*). The phenotype examined in a transgenic and knock out model is influenced by genetic background, which is the collection of all genes present in an organism that influence a trait or traits. The genes may be part of same biochemical or signaling pathway or of an opposing pathway or may appear unrelated to the gene being studied. Furthermore, allelic variations and the interactions between the allelic variants also influence a particular phenotype. These epigenetic effects can dramatically alter the observed phenotype and therefore can influence or alter the conclusions drawn form the transgenic or knockout models (Sigmund, Arterioscler. Throm. Vasc. Biol.20:1425-1429, 2000, see page 1425*; ref. of record*). The transgene expression and physiological consequences of transgene products in non-mouse mammals are not always accurately predicted among various species of mammals (Wall RJ Theriogenology 45:57-68, 1996:*; ref. of record*). Transgene efficiency is low, and range from 1% in farm animals (cattle, sheep, pigs) to 3% in laboratory animals like rabbits, mice and rats (Wall, see page 61). Furthermore, the lack of understanding of essential genetic control elements make it difficult to predict the behavior of a transgene in any and all animals because the expression is influenced by position effect in transgenic animals. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct and the site of integration, are the important factors that govern the expression of a transgene (Wall, page 61-62). The cis acting elements of one species may interact with different transactivating factors in other species. For example, the introduction of human growth

hormone transgene in mice results in mammoth mouse phenotype, where as expression of the same transgene in pig results in premature death of transgenic pigs. (Pursel VG et al J. Reprod Fert. Sup 40: 235-245 1990, see page 235, para.1; *ref. of record*). Furthermore, many biochemical pathways are plastic in nature, which reflects the ability of the embryo to use alternative gene when the preferred gene is modified. It is known in the art that the level and the specificity of a transgene as well as the phenotype of the transgenic animal are greatly dependent upon the specific expression vector used. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct and the site of integration, for example are the important factors that govern the expression of a transgene. (Kappel et al. Current Opinion in Biotechnology 3:558-553 1992; see page 550, col.1, para. 3-4, page 548, col.2 para.2; *ref. of record*).

Response to arguments

The applicant argues that that the specitication provides ample guidance enabling a skilled artisan to make and use the presently claimed transgenic mouse readily and without undue experimentation. The applicant argues that the present specification teaches nucleotide sequences (SEQ ID NO:1 and SEQ ID NO:3) which encode wild type mouse Fkh^{sf} (SEQ ID NO:2) and human Fkh^{sf} (SEQ ID NO:4) gene products. The applicant argues that the specification enables a skilled artisan to make transgenic mice whose cells express an Fkh^{sf} gene encoding a wild type gene product by injecting pronuclei with genomic DNA. The Applicant argues that the specification also provide guidance to analyze parameter related to the immune competence of the subject invention transgenic mice that express Fkh^{sf} transgene. The applicant concluded that in view of the direction and guidance provided by the instant specification, the present specification enables one skill in the art to make and use the claimed transgenic mouse without undue experimentation.

However, this is found NOT persuasive because applicant's argument alone cannot take place of evidence lacking in the record (see In re Scarbrough 182 USPQ, (CCPA) 1979). At best the specification as filed teaches "a transgenic Scurfy mouse whose somatic and germ cells express a transgene comprising a 30kb fragment of

normal genomic DNA, including ~7kb coding region of Fkh^{sf} gene as well as ~20kb of upstream flanking sequence and ~4kb of down stream sequences that contain a sequence encoding mouse Fkh^{sf} protein wherein the expression of exogenous Fkh^{sf} transgene results in reduction of T-lymphocyte proliferation in the scurfy mouse" (see spec page 33 lines 9-27). The specification as filed fails to disclose that a transgene encoding the mouse Fkh^{sf} (SEQ ID NO:2) or human Fkh^{sf} (SEQ ID NO:4) alone (without any promoter) would lead to the reduction of T-lymphocyte proliferation in the transgenic mouse as claimed. The specification fails to provided any substantial evidence that a transgene encoding human Fkh^{sf} (SEQ ID NO:4) would replace the function of normal mouse Fkh^{sf} gene, since the human and mouse Fkh^{sf}-polypeptide are only 87% identical.

Therefore considering the state of transgenic art and limited guidance provided in the instant specification (as filed), it is highly unpredictable that a transgene encoding mouse Fkh^{sf} polypeptide (SEQ ID NO:2) wherein the transgene has not been defined by structural and functional limitations would lead to the making transgenic mouse whose phenotype encompasses reduction in T-lymphocyte proliferation or responsiveness through CD3/CD28 costimulation (*see Pursel and Kappel).* Making a transgenic mouse wherein the transgene has not been identified by its structural and functional limitation is not considered routine in the art and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838 (**571-272-0769**). The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel Ph.D. can be reached on 703-305-1998 (**571-272-0781**). The fax phone numbers for the organization where this application or proceeding is assigned is **703-872-9306**. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S. Kaushal
Patent examiner

JEFFREY FREDMAN
PRIMARY EXAMINER